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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/972,177	10/05/2001	Laura C. Blumberg	PC11076A	3739

23913 7590 11/13/2003

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EXAMINER

COLEMAN, BRENDA LIBBY

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/972,177

Applicant(s)

BLUMBERG ET AL.

Examiner

Brenda L. Coleman

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-- Th MAILING DATE of this communication appears on the cover sheet with the corresponding address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 28 August 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I in Paper No. 4 is acknowledged.
2. Claims 1-14 are rejected as being drawn to an improper Markush group. The recited compounds, while possessing a common utility, differ widely in structure and are not art-recognized equivalents and are thus, independently distinct for the reasons set forth in the restriction requirement. The Markush group represented by the terms k, l, m and W have variably different definitions, rendering the claims clearly improper.

Priority

3. When a non-provisional application is entitled to an earlier U.S. effective filing date of one or more provisional applications under 35 U.S.C. 119(e), a statement such as "This application claims the benefit of U.S. Provisional Application No. 60/241,804, filed October 19, 2000." should appear as the first sentence of the description.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of "pro-drugs" is not adequately enabled.

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Applicants provide no guidance as to how the compounds are made more active in vivo. The choice of a "pro-drugs" will vary from drug to drug. Therefore, more than minimal routine experimentation would be required to determine which pro-drugs will be suitable for the instant invention.

5. Claims 9-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The scope of the method claims are not adequately enabled solely based on the inhibition of the chemokine receptor CCR1 provided in the specification. Evidence involving a single compound and two types of cancer was not found sufficient to establish the enablement of claims directed to a method of treating seven types of cancer with members of a class of several compounds. In re Buting 163 USPQ 689. The remarkable advances in chemotherapy have seen the development of specific compounds to treat specific types of cancer. The great diversity of diseases falling within the "tumor" category means that it is contrary to medical understanding that any agent (let alone a genus of thousands of compounds) could be generally effective against such diseases. The intractability of these disorders is clear evidence that the skill level in this art is low relative to the difficulty of the task.

Instant claim language embraces disorders not only for treatment, but, for prevention which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop cancer. There is no evidence of record, which would enable the skilled

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artisan in the identification of the people who have the potential of becoming afflicted with the disorders claimed herein.

There never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to treat cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied upon are reasonably predictive of in vivo efficacy by those skilled in the art. See *In re Ruskin*, 148 USPQ 221; *Ex parte Jovanovics*, 211 USPQ 907; MPEP 2164.05(a).

Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing

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out the mere germ of an idea does not constitute enabling disclosure. Genentech Inc. v. Novo Nordisk 42 USPQ2d 1001.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-14 are vague and indefinite in that it is not known what is meant by the variable "e" in the structure of formula I which is not defined within the claim.

b) Claims 1-14 are vague and indefinite in that it is not known what is meant by the period which follows the definition of k, l and m.

c) Claims 1 and 3-14 are vague and indefinite in that it is not known what is meant by the last moiety beginning on page 76 and ending in the first line of page 77 which is missing an open parenthesis, i.e. (C₁-C₆)alkoxycarbonyl)(C₁-C₆)alkylamino.

d) Claims 1 and 3-14 are vague and indefinite in that it is not known what is meant by the last moiety beginning in line 1 on page 77 and ending in line 2 of page 77 which is missing an open parenthesis, i.e. (C₁-C₆)alkoxycarbony)((C₁-C₆)alkyl)amino(C₁-C₆)alkyl.

e) Claims 1 and 3-14 are vague and indefinite in that it is not known what is meant by the last moiety beginning in line 1 on page 77 and ending in line 2 of page 77, i.e. (C₁-C₆)alkoxycarbony)((C₁-C₆)alkyl)amino(C₁-C₆)alkyl.

f) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the last moiety beginning in line 30 on page 77 and ending in line 31 of page 77 which includes an *, i.e. acetyl amino(C₁-*C₆)alkylcarbonylamino.

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g) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety in line 25 on page 78 which is followed by a semi-colon, i.e. carboxy(C₁-C₆)alkylcyanoguanidino;.

i) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety beginning in line 5 on page 79 and ending in line 6 of page 79 which appears to be missing a comma between what is believed to be two separate moieties, i.e. ((C₁-C₆)alkyl)₂amino(C₁-C₆)alkylamino(C₁-C₆)alkylcarbonylamino (C₁-C₆)alkylamino(C₁-C₆)alkylamino(C₁-C₆)alkylcarbonylamino.

j) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety beginning in line 14 on page 79 and ending in line 15 on page 79, i.e. (C₂-C₉)heteroaryloxycarbonylamino(C₁-C₆)alkylaminocarbonylaminol.

k) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety in line 34 on page 79, i.e. (C₂-C₉)heteroarylsulfonyl.

l) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the second occurrence of a comma after the moiety (C₂-C₉)heteroaryl(C₁-C₆)alkylamino in line 5 of page 80.

m) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety in line 13 of page 80 which is missing an open parenthesis, i.e. (C₃-C₁₀)cycloalkyl(C₁-C₆)alkyl)amino.

n) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety in line 22 of page 80 which is missing a close parenthesis, i.e. (aminocarbonyl(C₁-C₆)alkylaminocarbonyl).

o) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety beginning in line 22 on page 80 and ending in line 23 of page 80

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which is missing a close parenthesis, i.e. ((C₁-C₆)alkylaminocarbonyl(C₁-C₆)alkylaminocarbonyl.

p) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety beginning in line 23 on page 80 and ending in line 24 of page 80 which is missing a close parenthesis, i.e. ((C₁-C₆)alkoxycarbonyl(C₁-C₆)alkylaminocarbonyl.

q) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety beginning in line 24 on page 80 and ending in line 25 of page 80 which is missing a close parenthesis, i.e. (hydroxy(C₁-C₆)alkylaminocarbonylamidino.

r) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety beginning in line 34 on page 80 and ending in line 35 of page 80 which is missing an open parenthesis, i.e. (C₆-C₁₀)aryl(C₁-C₆)alkylaminocarbonyl)((C₁-C₆)alkyl)glycinamido.

s) Claims 1-5 and 8-14 are vague and indefinite in that it is not known what is meant by the moiety in line 8 of page 81 which is missing an open parenthesis, i.e. C₂-C₉)heteroaryl amino(C₂-C₆)alkoxy.

t) Claim 2 recites the limitation "(C₁-C₆)alkylcarbonyloxy" in the definition of R¹. There is insufficient antecedent basis for this limitation in the claim.

u) Claim 3 recites the limitation "(C₁-C₆)alkyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

v) Claim 5 recites the limitation "(C₁-C₆)alkyl" in the definition of Z. There is insufficient antecedent basis for this limitation in the claim.

w) Claim 6 recites the limitation "(C₂-C₉)heteroaryl (C₂-C₉)heteroaryloxy" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 14 of page 82.

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x) Claim 6 recites the limitation "carboxy(C₁-C₆)alkylaminocarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 15 of page 82.

y) Claim 6 recites the limitation "(C₂-C₉)heteroarylaminocarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See lines 15-16 of page 82.

z) Claim 6 recites the limitation "((C₁-C₆)alkylamino)(C₆-C₁₀)aryl(C₁-C₆)alkyl" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See lines 31-32 of page 82.

aa) Claim 6 recites the limitation "amino(C₁-C₆)alkoxycarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 32 of page 82.

ab) Claim 6 is vague and indefinite in that it is not known what is meant by the moiety beginning in line 36 on page 82 and ending in line 37 on page 82, i.e. ((C₁-C₆)alkyl)₂ amino(C₁-C₆)alkylcarbonylamino.

ac) Claim 6 recites the limitation "(C₁-C₆)alkyl and halo(C₁-C₆)alkyl" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 37 of page 82.

ad) Claim 6 recites the limitation "aminocarbonyl" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 2 of page 83.

ae) Claim 6 is vague and indefinite in that it is not known what is meant by the moiety in line 3 of page 83, i.e. aminocarbonyl(C₁-C₆)alkylaminocarbonyl.

af) Claim 6 recites the limitation "ureido(C₁-C₆)alkylcarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 4 of page 83.

ag) Claim 6 recites the limitation "(C₁-C₆)alkylcarbonylamino(C₁-C₆)alkylcarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 4 of page 83.

ah) Claim 6 recites the limitation "(C₁-C₆)alkylcarbonylamino(C₁-C₆)alkylaminocarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See lines 4-5 of page 83.

ai) Claim 6 is vague and indefinite in that it is not known what is meant by the second occurrence of ureido(C₁-C₆)alkylcarbonylamino which appears in line 4 and again in line 5 of page 83.

aj) Claim 7 recites the limitation "(C₂-C₉)heteroaryl (C₂-C₉)heteroaryloxy" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 11 of page 83.

ak) Claim 7 recites the limitation "carboxy(C₁-C₆)alkylaminocarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 12 of page 83.

al) Claim 7 recites the limitation "(C₂-C₉)heteroarylaminocarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See lines 12-13 of page 83.

am) Claim 7 recites the limitation "((C₁-C₆)alkylamino)(C₆-C₁₀)aryl(C₁-C₆)alkyl" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See lines 28-29 of page 83.

an) Claim 7 recites the limitation "amino(C₁-C₆)alkoxycarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 29 of page 83.

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ao) Claim 7 recites the limitation "aminocarbonyl" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 36 of page 83.

ap) Claim 7 is vague and indefinite in that it is not known what is meant by the moiety in line 36 of page 83, i.e. aminocarbonyl(C₁-C₆alkyaminocarbonyl).

aq) Claim 7 recites the limitation "ureido(C₁-C₆)alkylcarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 37 of page 83.

ar) Claim 7 recites the limitation "(C₁-C₆)alkylcarbonylamino(C₁-C₆)alkylcarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See line 37 page 83 through line 1 of page 84.

as) Claim 7 recites the limitation "(C₁-C₆)alkylcarbonylamino(C₁-C₆)alkylaminocarbonylamino" in the definition of R⁵. There is insufficient antecedent basis for this limitation in the claim. See lines 1-2 of page 84.

at) Claim 7 is vague and indefinite in that it is not known what is meant by the second occurrence of ureido(C₁-C₆)alkylcarbonylamino which appears in line 37 of page 83 and again in line 2 of page 84.

au) Claim 8 is vague and indefinite in that it is not known what is meant by "pamoatesalts".

av) Claims 10, 13 and 14 are substantial duplicates of claim 9, as the only difference is a statement of intended use which is not given material weight. Note In re Tuominen 213 USPQ 89.

aw) Claim 9 is vague and indefinite in that it is not known what is meant by "chronic obstructive pulmonary disease (COPD) allergic conditions". See lines 18-19 on page 84.

ax) Claim 11 is vague and indefinite in that it is not known what is meant by "chronic obstructive pulmonary disease (COPD) allergic conditions". See lines 9-10 on page 85.

ay) Claim 13 is vague and indefinite in that it is not known what is meant by "chronic obstructive pulmonary disease (COPD) allergic conditions". See line 37 on page 85 through line 1 on page 86.

az) Claims 9-14 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by a chemokine receptor. It is unclear which diseases are associated with each of the chemokine receptors. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One can not conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage

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regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a drug, particularly in cancer and CNS diseases, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in

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antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 703-305-1880. The examiner can normally be reached on 8:30-5:00 Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

A handwritten signature in cursive script that reads "Brenda Coleman". The signature is written in dark ink and includes a long, sweeping horizontal stroke at the end.

Brenda Coleman
Primary Examiner Art Unit 1624
November 10, 2003